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(54) Title: TRICLOSAN AND SILVER COMPOUND CONTAINING MEDICAL DEVICES

(57) Abstract

The present invention relates to polymeric medical articles comprising combinations of triclosan and silver-containing compounds. It is based, at least in part, on the discovery that these agents act synergistically, thereby permitting the use of relatively low levels of both agents. While it had been previously found that triclosan can be particularly useful when used in conjunction with chlorhexidine, it has been further discovered that medical articles having suitable antimicrobial properties may be prepared, according to the present invention, which contain triclosan without chlorhexidine. Such medical articles offer the advantage of preventing or inhibiting infection while avoiding undesirable adverse reactions to chlorhexidine by individuals that may have sensitivity to chlorhexidine.

TRICLOSAN AND SILVER COMPOUND CONTAINING MEDICAL DEVICES

SPECIFICATION

1.0 INTRODUCTION

The present invention relates to medical devices comprising synergistic combinations of triclosan and silver containing compounds.

2.0 BACKGROUND OF THE INVENTION

Whenever a medical device comes in contact with a patient, a risk of infection is created. Thus, a contaminated examination glove, tongue depressor, or stethoscope could transmit infection. The risk of infection dramatically increases for invasive medical devices, such as intravenous catheters, arterial grafts, intrathecal or intracerebral shunts and prosthetic devices, which not only are, themselves, in intimate contact with body tissues and fluids, but also create a portal of entry for pathogens.

A number of methods for reducing the risk of infection have been developed which incorporate anti-infective agents into medical devices, none of which have been clinically proven to be completely satisfactory. Such devices desirably provide effective levels of anti-infective agent during the entire period that the device is being used. This sustained release may be problematic to achieve, in that a mechanism for dispersing anti-infective agent over a prolonged period of time may be required, and the incorporation of sufficient amounts of anti-infective agent may adversely affect the surface characteristics of the device. The difficulties encountered in providing effective antimicrobial protection increase with the development of drug-resistant pathogens.

One potential solution to these problems is the use of a synergistic combination of anti-infective agents that requires relatively low concentrations of individual anti-infective agents which may have differing patterns of bioavailability.

coated with microcrystalline wax. Antimicrobial agents such as chlorhexidine or triclosan may be incorporated into the coated floss.

United States Patent No. 5,200,194 by Edgren et al. relates to an oral osmotic device comprising a thin semipermeable membrane wall surrounding a compartment housing a "beneficial agent" (that is at least somewhat soluble in saliva) and a fibrous support material composed of hydrophilic water-insoluble fibers. The patent lists a wide variety of "beneficial agents" which may be incorporated into the oral osmotic device, including chlorhexidine and triclosan.

United States Patent No. 5,019,096 by Fox, Jr., et al. relates to infection-resistant medical devices comprising a synergistic combination of a silver compound (such as silver sulfadiazine) and chlorhexidine.

International Patent Application No. PCT/GB92/01481, Publication No. WO 93/02717, relates to an adhesive product comprising residues of a copolymerisable emulsifier comprising a medicament, which may be povidone iodine, triclosan, or chlorhexidine.

International Patent Application No. PCT/US96/20932, Publication No. WO 97/25085, relates to polymeric medical articles comprising synergistic combinations of chlorhexidine and triclosan which utilize relatively low levels of these agents.

In contrast to the present invention, none of the above-cited references teach medical articles comprising synergistic combinations of triclosan and silver compounds which utilize relatively low levels of these agents and provide effective levels of antimicrobial activity, even in the absence of chlorhexidine.

3.0 SUMMARY OF THE INVENTION

The present invention relates to polymeric medical articles comprising combinations of triclosan and/or other chlorinated phenols and silver-containing compounds. It is based, at least in part, on the discovery that these agents act synergistically, thereby permitting the use of relatively low levels of both agents. While it had been previously found that triclosan can be particularly useful when used in conjunction with chlorhexidine, it has been further discovered that medical articles

As shown in Example Sections 7, 9-17 and 19, medical articles, which may be hydrophilic or hydrophobic, treated with combinations of triclosan and various silver compounds exhibit desirable antimicrobial properties. As shown in Example Sections 8, 13 and 14 such articles exhibit smooth surfaces that tend to resist bacterial adherence, which may be at least partly responsible for their antimicrobial quality.

The present invention provides for medical articles treated with chlorinated phenols other than triclosan in combination with one or more silver compound. As shown in Example Section 18, such combinations result in enhanced antimicrobial activity. Suitable chlorinated phenols include parachlorometaxylenol ("PCMX") and dichlorometaxylenol ("DCMX"). The amount of chlorinated phenol which may be used is as set forth below for triclosan, but may be adjusted for differences in potency when tested against a particular microbe. For example, in specific, non-limiting embodiments of the invention polymeric medical articles may be prepared using treatment solutions comprising between about 0.1 and 5 percent, preferably between about 0.3 and 1.5 percent, of a silver compound, and between about 0.1 and 20 percent, preferably between about 0.1 and 8 percent, of a chlorinated phenol, preferably PCMX. The present invention also provides for medical articles comprising triclosan in addition to another chlorinated phenol.

In additional embodiments, the present invention provides for medical articles having anti-infective activity which comprise triclosan and/or another chlorinated phenol, a silver compound, and an anti-inflammatory agent. It has been found that the addition of an anti-inflammatory compound enhances the antimicrobial activity of such devices (see Section 17 below).

In still further embodiments, the present invention provides for medical articles which have been treated with a hydrogel, and further comprise a metal compound.

The term triclosan ("TC"), as used herein, refers to a compound also known as 2,4,4'-trichloro-2'-hydroxydiphenyl ether and also known as 5-chloro-2-(2,4-dichlorophenoxy)phenol.

about 0.1 and 20 percent and preferably between about 0.1 and 8 percent of triclosan and/or other chlorinated phenol; (2) treatment solutions comprising between about 0.1 and 10 percent, and preferably between about 1 and 5 percent of one or more hydrophilic or hydrophobic polymer; between about 0.1 and 5 percent, and preferably between about 0.3 and 1.5 percent of a silver compound; and between about 0.1 and 20 percent, and preferably between about 0.1 and 8 percent of triclosan and/or other chlorinated phenol; (3) polymer-containing medical articles treated with a treatment solution as set forth in (1) or (2) above, and articles physically equivalent thereto (that is to say, articles prepared by a different method but having essentially the same elements in the same proportions); (4) polymer-containing medical articles treated with treatment solutions set forth in (1) or (2) above wherein the articles are dried and thereafter coated with an anti-infective and/or polymeric coating in accordance with a two-step process. The treatment solutions set forth in (1) or (2) may optionally further comprise (i) an organic acid, at a concentration of between about 0.1 and 5 percent, preferably between about 0.1 and 2 percent; (ii) an anti-inflammatory agent, at a concentration of between about 1 and 5 percent, preferably between about .1 and 1 percent; (iii) an antimicrobial other than a silver compound or triclosan at a concentration of between about 0.1 and 10 percent; and/or (iv) a hydrogel at a concentration of between about 0.5 to 10 percent, preferably between about 1 and 5 percent. In preferred non-limiting embodiments of the invention, the amount of silver present as silver atom or silver ion is about 0.9%. In preferred non-limiting embodiments of the invention, the treatment solution and/or medical article does not contain chlorhexidine or a chlorhexidine salt. The medical articles are "treated" by exposing them, for an effective period of time, to the treatment solution, where an "effective period of time" is that period of time sufficient to introduce anti-infective quantities of triclosan and/or other chlorinated phenol and silver compound. Where the concentration of triclosan and/or other chlorinated phenol in the treatment solution is between 0.1 and 8 percent, the effective period of time may be between about 30 seconds and one hour; where the concentration of tricolsan and/or other chlorinated phenol in the treatment solution is between about 9 and 20 percent, the effective period of time may be between about 10 seconds and 2 minutes. Longer periods of

Polymers, triclosan, and silver compounds used according to the invention may be sparingly soluble in certain solvents or solvent mixtures. It therefore may be desirable to first dissolve the relevant material in a solvent or component of a solvent system which favors dissolving. For example, where polyurethane, triclosan, and a silver compound are desirably incorporated into an alcohol/tetrahydrofuran ("THF") solvent system, the polyurethane may first be dissolved in THF and the triclosan and silver compound may be dissolved in alcohol (in certain instances with the addition of an aqueous solution of ammonia (referred to interchangeably herein as either ammonia, ammonium hydroxide, or NH_3) to facilitate solubilization of the silver compound), before the THF and alcohol components are mixed. The use of a solvent system comprising ammonia may be particularly desirable when a silver salt is used.

4.1 HYDROPHILIC ARTICLE TREATED WITH A SOLUTION OF A HYRDOPHILIC POLYMER

In one particular set of non-limiting embodiments, the present invention provides for a hydrophilic polymeric medical article (*i.e.*, a medical article fabricated from a hydrophilic polymer) treated by coating, dipping or soaking the article in a treatment solution of a hydrophilic polymer comprising a silver compound and triclosan (and/or other chlorinated phenol) wherein the silver compound and triclosan or other chlorinated phenol are present in amounts such that their combination, in the treated article, has effective anti-microbial activity. The term "effective antimicrobial activity" refers to an ability to decrease the number of colony-forming units of a bacterium or yeast, in a 24 hour period, by a factor of ten or more and preferably a factor of 100 or more. The terms "treat", "treated", etc., as used herein, refer to coating, impregnating, or coating and impregnating a medical article with anti-infective agent. The term "hydrophilic polymer", as used herein, refers to polymers which have a water absorption greater than 0.6 percent by weight (and, in preferred embodiments, less than 2 percent by weight; as measured by a 24 hour immersion in distilled water, as described in ASTM Designation D570-81) including, but not limited to biomedical polyurethanes (*e.g.*, ether-based polyurethanes and ester-based polyurethanes, as set forth in Baker, 1987, in *Controlled Release of Biologically*

percent, and preferably between about 1 and 5 percent, of a polyurethane - silicone copolymer; (ii) between about 0.1 and 5 percent, and preferably between about 0.3 and 1.5 percent, of a silver compound; and (iii) between about 0.1 and 20 percent, and preferably between about 0.1 and 8 percent, of triclosan and/or other chlorinated phenol.

4.3 HYDROPHOBIC ARTICLE TREATED WITH A SOLUTION OF A HYDROPHOBIC POLYMER

In another set of particular non-limiting embodiments, the present invention provides for a hydrophobic polymeric medical article treated by coating, dipping or soaking the article in a treatment solution of hydrophobic polymer comprising a silver compound and triclosan and/or other chlorinated phenol, wherein the silver compound and triclosan and/or other chlorinated phenol are present in amounts such that their combination, in the treated article, has effective antimicrobial activity. In one specific, non-limiting embodiment, the medical article is a silicone catheter or a polyvinylchloride catheter which has been dipped or soaked in a treatment solution comprising (i) between about 0.1 and 10 percent, and preferably between about 1 and 5 percent, of a silicone polymer; (ii) between about 0.1 and 5 percent, and preferably between about 0.3 and 1.5 percent, of a silver compound; and (iii) between about 0.1 and 20 percent, and preferably between about 0.1 and 8 percent, of triclosan and/or other chlorinated phenol.

4.4 HYDROPHOBIC ARTICLE TREATED WITH A SOLUTION OF A HYDROPHILIC POLYMER

In yet another set of particular non-limiting embodiments, the present invention provides for a hydrophobic polymeric medical article treated by coating, dipping or soaking the article in a treatment solution of hydrophilic polymer comprising a silver compound and triclosan and/or other chlorinated phenol, wherein the silver compound and triclosan and/or other chlorinated phenol are present in amounts such that their combination, in the treated article, has effective anti-microbial activity. In a specific, non-limiting embodiment, the medical article is a silicone catheter or Teflon graft which has been dipped, coated or soaked in a treatment

The treatment solutions may comprise between about 0.1 and 10 percent (w/v), and preferably between about 1 and 5 percent (w/v), of one or more dissolved polymer (*e.g.*, one or more species of polyurethane, silicone, or hydrogel). Preferred soaking times according to the one-step method vary between 15 seconds and 1 hour, depending upon the polymer selected. A shorter soaking time in a drug/solvent system is preferred since it is less likely to negatively affect the physical integrity of the polymeric device, particularly polyurethane catheters. In order to attain a sufficient drug uptake using a shorter soaking time, it is preferred that the amount of triclosan or other chlorinated phenol in the treatment solution be between about 10 and 20 percent (w/v). For a specific example of a method that uses higher levels of triclosan and a shorter soaking time see Section 9 below.

If a hydrophobic polymeric medical article is to be impregnated with a silver compound and triclosan and/or other chlorinated phenol, the impregnating solution may, in specific non-limiting embodiments, comprise the following (percentages of solvents in this paragraph being volume/volume (v/v) except where noted to be weight/volume (w/v)): 10% methanol /90% THF; 10% ethanol/90% THF; 10% reagent alcohol/90% THF; 10% ethanol/10% ammonia/80% THF; 10% reagent alcohol/10% ammonia/80% THF; 30% ethanol/70% THF; 30% reagent alcohol/70% THF; 30% methanol/70% THF; 1-5 percent (w/v) silicone polymer in 10% methanol/90% THF; 1-5 percent (w/v) silicone polymer in 10% ethanol/90% THF; 1-5 percent (w/v) silicone polymer in 10% reagent alcohol/90% THF; 1-2 percent (w/v) polylactic acid in 10% methanol/90% THF; 1-2 percent w/v polylactic acid in 10% ethanol/90% THF; 1-2 percent (w/v) polylactic acid in 10% reagent alcohol/90% THF; 1-5 percent (w/v) silicone polymer in 30% methanol/70% THF; 1-5 percent (w/v) silicone polymer in 30% ethanol/70% THF; 1-5 percent (w/v) silicone polymer in 30% reagent alcohol/70% THF; 1-2 percent (w/v) polylactic acid in 30% methanol/70% THF; 1-2 percent (w/v) polylactic acid in 30% ethanol/70% THF; 1-2 percent (w/v) polylactic acid in 30% reagent alcohol/70% THF; 1-5 percent (w/v) silicone polymer in 100% methyl ethyl ketone; and 1-2 percent (w/v) polyurethane in 30% ethanol/70% THF. In general, such treatment solutions may comprise between 0.1 and 10 percent, and preferably between about 1 and 5 percent, of one or more

4.7 MEDICAL ARTICLES HAVING ANTI-ADHERENT PROPERTIES

It has been discovered that medical articles treated with mixtures of silver compounds and triclosan exhibit anti-adherent qualities and anti-microbial effectiveness, even in the absence of chlorhexidine. While not being bound to any particular theory, it is believed that triclosan and silver compounds form a triclosan-silver compound complex, such that impregnation of this triclosan-silver compound complex into medical articles increases resistance to microbial adherence to the surfaces by rendering the surfaces smooth and shiny. It has further been discovered that the combination of silver compounds and other compositions, such as other chlorinated phenolic compounds, anti-inflammatory agents, hydrophilic and hydrophobic polymers and hydrogels each separately contribute to enhanced and prolonged antimicrobial efficacy of the antimicrobial agents. The synergistic combinations of triclosan and silver compounds that are sparingly soluble are especially suitable for forming a smooth surface and for providing a sustained and prolonged release of anti-microbial agents.

In a specific example of a method of direct impregnation of triclosan and a silver compound into a Dacron device, a treatment solution may be prepared including 1 to 6 percent triclosan and 0.1 to 0.2 percent of a silver compound in a solvent mixture containing (v/v) 10 percent ammonia, 10 percent alcohol and 80 percent THF. The device may be soaked for 1 to 10 minutes, dried and rinsed. In variations of this example, between about 1 and 10 percent of a hydrophilic polymer or a hydrophobic polymer may be included in the treatment solution. Suitable hydrophilic polymers include, but are not limited to, one or more of polyurethane, polycaprolactone, and polyactic acid. Suitable hydrophobic polymers include, but are not limited to, silicone polymers.

4.8 MEDICAL ARTICLES COMPRISING TRICLOSAN, A SILVER COMPOUND, AND AN ANTI-INFLAMMATORY AGENT

Anti-inflammatory agents such as salicylic acid, paraaminosalicylic acid, and acetylsalicylic acid were impregnated along with triclosan and a silver compound into medical devices to reduce inflammatory reaction around the wound at the insertion site and thus enhance wound healing. Surprisingly, it has been

These agents used in addition to the triclosan and/or other chlorinated phenol and silver compound combination provide an effective broad spectrum anti-microbial field of activity initially, which inactivates pathogens that otherwise can heavily contaminate the sterile field during implantation. For a non-limiting specific example, see Section 15.

The anti-adherent surface of these devices continues to prevent adherence of microbes that may enter the device tract during and subsequent to implantation. Once these additional agents are diffused out of the devices, the anti-adherent surface continues to prevent adherence of microbes which may contact the device surface through hematogenous seeding or contaminated infusate. Further, without being bound to any particular theory, it is believed that sustained and prolonged release of the anti-microbial agents occurs from the putative triclosan-silver compound complex which provides a longer period of protection.

4.10 MEDICAL ARTICLES COMPRISING A HYDROGEL

According to the present invention, it has been determined that the use of hydrogel polymers increases the antimicrobial efficacy of hydrophilic or hydrophobic matrix systems. In a particular embodiment, the present invention provides for a hydrophilic or hydrophobic medical article which has been impregnated, coated or impregnated and coated with a treatment solution comprising (i) a hydrophilic or hydrophobic polymer, (ii) one or more metal compounds comprising metal atoms or ions or complexes comprising a metal atom or ion selected from the group consisting of silver, copper, zinc, calcium, aluminum and magnesium, (iii) triclosan or other chlorinated phenol, and (iv) a hydrogel. Such medical articles may further comprise, or the treatment solution may comprise, a biguanide such as chlorhexidine or a chlorhexidine salt. In other embodiments, the present invention provides for a metallic or ceramic medical article coated with a treatment solution of (i) to (iv) as set out above. In a preferred embodiment, the hydrogel comprises polyvinyl pyrrolidone ("PVP"). In another preferred embodiment, the hydrophobic polymer polyvinyl chloride ("PVC") may be used to create a hydrophobic matrix into which PVP and antimicrobial agents may be impregnated. Other useful hydrogels that

TABLE 1

Silver Carbonate (μmole)	Ammonia (μmole)	Triclosan (μmole)	Solubility
10	100	0	Not Soluble
10	200	0	Not Soluble
10	300	0	Not Soluble
10	400	0	Not Soluble
10	0	30	Not Soluble
10	50	10	Partially Soluble
10	100	10	Partially Soluble
10	150	10	Soluble
10	75	20	Partially Soluble
10	50	30	Soluble

TABLE 2

Silver oxide (μmole)	Ammonia (μmole)	TC (μmole)	Solubility (μmole)
10	10	0	Not soluble
10	100	0	Soluble
10	10	10	›90% Soluble
10	10	20	Soluble

6.0 EXAMPLE: EVALUATION OF THE ANTI-MICROBIAL EFFICACY OF TRICLOSAN-SILVER COMPOUND COMBINATIONS IN BROTH CULTURES

The synergistic anti-microbial efficacy of the triclosan/silver compound combination, triclosan/silver sulfadiazine, is illustrated by the results shown in Table 3, and were determined by the following protocol. Drug solutions containing 10% ammonia were prepared in alcohol, and 0.1 ml of each solution was added to 0.9 ml of bacterial culture (50% trypticase soy broth + 50% Bovine Calf Serum containing 10^8

sulfadiazine from 0.5 to 1.0 in the presence of 0.5 triclosan resulted in a 1 log reduction in growth in culture, whereas the increase of 0.5 to 1.0 percent silver sulfadiazine in the absence of triclosan did not result in a significant decrease. The cell growth in culture in the presence of 0.5 percent triclosan alone added to the cell growth in culture in the presence of 0.5 percent of silver sulfadiazine, the combined presence of 0.5 triclosan and 1.0 silver sulfadiazine resulted in a 3 log reduction in growth in culture, and the increase of 0.5 to 1.0 percent silver sulfadiazine compared to the growth in culture at .5 percent triclosan results in a 1 log decrease.

The effects of triclosan and silver carbonate combinations on *S. aureus* growth in culture were also determined using the same protocol. The results are presented in Table 4.

TABLE 4

Solution		Growth in Culture
Triclosan (%)	Silver Carbonate (%)	(cfu/ml)
0	0	5×10^7
.25	0	2×10^7
.5	0	1.2×10^7
0	.06	1×10^5
0	.125	2×10^3
0	.25	5×10^2
.5	.06	3.2×10^4
.5	.125	0
.5	.25	0

The results shown in Table 4 illustrate the synergistic activity of triclosan and silver carbonate. In the control, in the absence of both triclosan and silver carbonate the growth in cell culture was of the magnitude of 5×10^7 cfu/ml. Combining 0.5 percent triclosan and 0.25 percent silver carbonate resulted in a 7 log reduction in growth in culture. The addition of 0.5 percent triclosan alone resulted in a 0 log reduction, and the addition of 0.25 silver carbonate alone resulted in a 5 log reduction. Therefore one would expect a 5 log reduction of growth in cell culture

chlorhexidine at concentrations set forth in Table 6.

The zones of inhibition were studied against *S. epidermidis* and *P. aeruginosa* over a two day period. The results, shown in Tables 5 and 6, indicate that the combination of citric acid, triclosan and silver compound (silver carbonate) resulted in superior antimicrobial activity against *Pseudomonas aeruginosa,* compared to other organic acids tested.

TABLE 5

Treatment Solution	Zones of Inhibition (mm)			
	S. epidermidis		*P. aeruginosa*	
	Day 1	Day 2	Day 1	Day 2
6% TC + 0.6% Ag_2CO_3 +3% 93A PU + 1% 60D PU	20	18	9	0
6% TC + 0.6%Ag_2CO_3 + 2% salicylic acid + 3% 93A PU + 1% 60D PU	20	18	11	0
6% TC + 0.6%Ag_2CO_3 + 2% mandelic acid + 3% 93A PU + 1% 60D PU	20	18	8	0
6% TC + 0.6%Ag_2CO_3 + 2% deoxycholic acid + 3% 93A PU + 1% 60D PU	20	18	8	0
6% TC + 0.6%Ag_2CO_3 + 2% citric acid + 3% 93A PU + 1% 60D PU	20	19	11	8
6% TC + 0.3%Ag_2CO_3 + 2%CHX + 3% 93A PU + 1% 60D PU	21	20	13	12

Method C: The ends of the catheter segments were sealed and the segments were dipped in a treatment solution of 70% v/v THF (containing 60D polyurethane) + 30% v/v reagent alcohol having a final concentration of 2% w/v 60D polyurethane. The catheter segments were then dried for one hour, and then were soaked for 5 minutes in a treatment solution of 90% v/v (8:1 ethanol/ammonia containing triclosan and silver compound) + 10% THF, having final concentrations of 6% w/v triclosan and 0.3% silver (the treatment solution used in Method B).

Method D: Catheter segments were dipped in a treatment solution of 70% v/v THF (containing 93A polyurethane and 60D polyurethane) + 30% v/v (2:1 reagent alcohol:ammonia containing a silver compound), having final concentrations of 3% w/v 93A polyurethane, 1% w/v 60D polyurethane, and 0.3% w/v silver (atom or ion) (the treatment solution used in Method A, but without the triclosan).

The surface characteristics of catheter segments treated according to Methods A-D are shown in Table 7.

TABLE 7

Silver Salt	Surface Characteristics			
	A	B	C	D
0 (only triclosan)	3	3	4	—
Silver carbonate	4	4	4	3
Silver deoxycholate	4	4	4	Rough
Silver oxide	4	4	4	3
Silver salicylate	4	4	4	2
Silver iodide	3	3	3	2
Silver sulfadiazine	3	2	2	2
Silver nitrate	4	4	4	4

Table 8 shows the results when the outer surfaces of catheter segments were impregnated by dipping the catheters in a treatment solution of 70 % v/v THF (containing 93A and 60D polyurethanes) and 30% v/v reagent alcohol (containing

concentration was reduced to 6% and the soaking time was increased to 1 minute. The initial drug levels, measured spectrophotometrically, and zones of inhibition against *S. epidermidis* and *P. aeruginosa* were determined for catheter samples of both groups and are shown in Table 9.

TABLE 9

Treatment	µg TC/cm	Zones of Inhibition (mm) vs. *S. epidermidis*	vs. *P. aeruginosa*
15 sec x (15% TC + 0.48% $AgNO_3$)	436	11	4
1 min x (6% TC + 0.48% $AgNO_3$)	410	13	4

As illustrated in Table 9, both initial drug uptake and zone of inhibition data indicate that a similar efficacy is obtainable using a higher concentration of drug and a shorter soaking time. In addition, a shorter soaking time in a drug/solvent system is less likely to negatively affect the physical integrity of the device.

10.0 EXAMPLE: IMPREGNATION OF TRICLOSAN-SILVER COMBINATION IN LATEX URINARY CATHETER AND PTFE SOFT TISSUE PATCHES (STP)

Segments of latex urinary catheters and PTFE soft tissue patches (STP) were impregnated by soaking these materials (or suctioning under vacuum in the case of PTFE STP) for 1 hour in a treatment solution prepared by mixing 80% v/v THF and 10% v/v reagent alcohol/10% v/v ammonia (containing triclosan and silver carbonate), having final concentrations of 1% w/v triclosan and 0.2% w/v silver carbonate. The impregnated materials were dried and then rinsed in water and dried again. The antimicrobial properties of the material were then tested by measuring the zones of inhibition produced against *S. aureus*, *P. aeruginosa*, *E. aerogenes* and *C. albicans* after placing the treated material on a trypticase soy agar plate seeded with

12.0 EXAMPLE: METHOD OF IMPREGNATION OF LEFT VENTRICULAR ASSIST DEVICE (LVAD) DRIVE LINES

Left ventricular assist device (LVAD) drive lines, which are made of Dacron material and are attached to silicone tubing, were impregnated with a polymeric matrix containing triclosan and silver salts.

Dacron material was treated with one of two different treatment solutions as follows.

In a first case, Dacron material was uniformly spread with a treatment solution which was 10% v/v ammonia, 10% v/v alcohol (containing silver carbonate and triclosan) + 80% THF (containing 93A and 60D polyurethanes), having final concentrations of 0.2% w/v silver carbonate, 0.1% w/v triclosan, 4% w/v 93A polyurethane, and 1% w/v 60D polyurethane. As in previous examples, the silver carbonate and triclosan were first dissolved in 1:1 ammonia/alcohol, and the polyurethanes were first dissolved in THF, and then the ammonia/alcohol and THF were mixed to achieve the proper final ratios.

In a second case, Dacron material was uniformly spread with a treatment solution which was 10% v/v ammonia, 10% v/v alcohol (containing silver carbonate, triclosan and chlorhexidine) + 80% THF (containing 93A and 60D polyurethanes), having final concentrations of 0.2% w/v silver carbonate, 0.5% w/v chlorhexidine, 0.1% w/v triclosan, 4% w/v 93A polyurethane, and 1% w/v 60D polyurethane.

Dacron material having a polymer-drug film prepared as above was then attached to silicone tubing, thereby creating a drive line, and dried. This method is particularly important for devices in which tissue ingrowth is intended to occur after implantation (*e.g.*, cuffs). Antimicrobial activity was evaluated after 24 hours by measuring the zones of inhibition produced by placing 0.25 cm length of drive line on trypticase soy agar seeded with 0.3 ml of 10^8 cfu/ml bacteria and incubated at 37°C for 24 hours. The zones of inhibition were measured after 24 hours, and the results are shown in Table 12.

bacterial cultures, and then measuring the amount of bacteria adhered to the extracted catheter segments.

The catheter segments were impregnated with triclosan and various silver compounds and/or chlorhexidine diacetate (CHA), using treatment solutions having the final concentrations of agents set forth in Table 14, below. In each case, the amount of silver compound in the treatment solution contributed silver atom/ion at a concentration of 0.3% w/v. The treatment solutions comprised THF and reagent alcohol mixed solutions, where polyurethane components were dissolved in the THF and triclosan and silver compounds were dissolved in the reagent alcohol prior to mixing. The amount of THF/polyurethane was generally 70% (v/v). The amount of reagent alcohol was 30% (v/v). Where indicated by an asterisk in Table 16, the solvent was simply reagent alcohol; otherwise, the solvent system was reagent alcohol/ammonia in a 2:1 ratio (accounting for 20% and 10%, respectively, on a volume to volume basis). Polymers in the treatment solutions were initially dissolved in the THF component and had final concentrations of 3% w/v 93A polyurethane and 1% w/v 60D polyurethane. Catheter segments were dipped in the treatment solution, and then dried for three days prior to use. Unimpregnated catheter segments were used as controls.

Six 3 cm segments of catheters from each catheter group were implanted in a subcutaneous pocket on the dorsal side of laboratory rats. After seven days the catheters were removed and rinsed twice in saline and processed as follows: Each group of catheter segments (6 x 3 cm) were transferred to 18 ml of 10% BCS [?]+ 90% TSB containing 3.0ml of 10^7 cfu *S. epidermidis*/ml at 37°C in a rotary shaker for 4 hours. Then the catheters were removed, blotted, rinsed twice in saline, blotted and rolled over the surface of drug neutralizing agar plates (D/E plates) and incubated for 24 hrs at 37°C. The colony counts observed in Table 14 were then determined for each catheter group.

As evidenced from the results of Table 14, the catheter groups containing triclosan-silver salt combinations were effective in preventing bacterial adherence on catheters after being implanted for seven days in rats.

A further two sets of experiments were carried out to determine the antimicrobial efficacy of catheters treated according to the invention. In particular, one set of experiments involved an "initial infection model" where the initial catheter wound site was inoculated with bacteria, and another set of experiments involved a "delayed infection model" in which catheters implanted in rats for ten days were removed and exposed to bacterial cultures *in vitro*. In these two sets of experiments, the results of which are shown in Table 15, long term and short term efficacy of treated catheters was evaluated and compared.

In experiments involving the "initial infection model", the dorsal side of a rat was shaved and a 7 cm segment of catheter treated with the agents set forth in Table 15 (with both ends sealed with silicone plugs) was implanted subcutaneously through a 0.5 cm incision just above the shoulder area. The catheter was kept in place, and the tract and insertion site were inoculated with 20 µl of bacterial culture having 10^8 cfu of *S. aureus* per milliliter. The wound was then closed with surgical clips. After ten days, the catheters were removed and swab cultures of the insertion site and tract were taken. Bacterial adherence on the outer surface of the catheters was determined by sonicating the catheters in drug neutralizing media and then subculturing on a trypticase soy agar plate.

In experiments involving the "delayed infection model", catheter segments (3 cm each, with sealed ends, treated with the agents set forth in Table 15) were implanted subcutaneously in rats (6 segments of catheters treated with the same agents per rat). After ten days *in vivo*, the catheters were excised and rinsed twice with saline. Then each group of six segments was incubated in 18 ml of a log-phase culture of *S. epidermidis* (10^7 cfu/ml of 10% bovine adult serum + 90% TSB) in a rotary shaker for four hours. The bacterial adherence was determined by sonicating the catheters in drug neutralizing media and then subculturing on a trypticase soy agar plate.

1:1 reagent alcohol/ammonium hydroxide, and then mixing with THF to produce a 80% v/vTHF, 10% reagent alcohol, 10% v/v ammonium hydroxide solution having triclosan, chlorhexidine, and silver carbonate final concentrations as specified in Table 16 below. The patch material was soaked in treatment solution for 1 hour under a vacuum. The patches were implanted subcutaneously in a pocket in the abdominal area of rats and infected with 10 µl of 10^8 CFU *S. aureus*. After 7 days, they were removed and bacterial adherence was determined by sonicating the catheters in drug neutralizing media and then subculturing on a trypticase soy agar plate. The efficacy of patches in resisting infection due to contamination at the time of implantation is illustrated by the bacterial adherence data provided in Table 16.

TABLE 16

Impregnation Solution	Bacterial Adherence CFU/DISK
0.25%TC + 0.2%Ag_2CO_3 +0.5 CHX	4
1.0%TC + 0.2%Ag_2CO_3	1
0.5%CHX + 0.2%Ag_2CO_3	15
0.5%TC + 0.25%CHA + 0.25%CHX	15
Unimpregnated	7.6 X 10^3

As shown in Table 16, all of the above groups with and without chlorhexidine were observed to be similarly efficacious relative to the control, unimpregnated group.

15.0 EXAMPLE: ENHANCEMENT OF THE ANTI-MICROBIAL ACTIVITY OF DEVICES CONTAINING SILVER AND TRICLOSAN USING OTHER SOLUBLE ANTI-INFECTIVE AGENTS

Polyurethane catheter segments were impregnated by dipping in a treatment solution prepared by mixing 10%v/v ammonia/20%v/v reagent alcohol (containing triclosan, silver carbonate, and, except for the control, an additional antibiotic) with 70% v/v THF (containing 93A and 60D polyurethanes), having final

16.0 EXAMPLE: ANTIMICROBIAL ACTIVITY OF VARIOUS TRICLOSAN - SILVER COMPOUND COMBINATIONS

Polyurethane catheter segments were treated by dipping in a treatment solution having final concentrations of triclosan and/or silver compound as set forth in Table 11, below. Six catheter segments from each group were placed vertically on a trypticase soy agar plate seeded with 0.3 ml of 10^8 cfu/ml bacterial/yeast culture and incubated at 37°C for 24 hours. The results are shown in Table 18.

It is noted that the combination of triclosan with either silver paraaminobenzoate, silver paraaminosalicylate, or silver acetylsalicylate resulted in unexpected efficacy against *C. albicans* as compared with each of the agents tested alone. Also illustrated by Table 18 is the synergistic effect achieved by the presence of triclosan in combination with silver salts.

17.0 EXAMPLE: IMPREGNATION OF ANTI-INFLAMMATORY AGENTS ALONG WITH TRICLOSAN AND SILVER SALTS

The following experiments demonstrated that the addition of the anti-inflammatory agent salicylic acid and its derivatives to combinations of triclosan and silver compounds improved antimicrobial activity.

LVAD drive lines made of Dacron were impregnated with triclosan, silver sulfadiazine and chlorhexidine, with or without salicylic acid, as follows. One set of pieces of Dacron were uniformly spread with a treatment solution prepared by mixing 30% v/v alcohol (containing triclosan (TC), silver sulfadiazine (AgSD), and chlorhexidine (CHX)) and 70% v/v THF (containing 93A and 60D polyurethanes), having final concentrations of 0.1% w/v triclosan, 0.2% w/v silver sulfadiazine, 0.5% w/v chlorhexidine, 4% w/v 93A polyurethane, and 1% w/v 60D polyurethane. Another set of Dacron pieces were uniformly spread with a second treatment solution having the same components, but also having a final concentration of 0.5% w/v salicylic acid (the salicylic acid being initially dissolved in the ethanol component). As a control, one set of Dacron pieces was treated with a third treatment solution containing salicylic acid and polymer but lacking triclosan, silver sulfadiazine, and chlorhexidine. The Dacron pieces were dried for 24 hours prior to antimicrobial testing.

In an analogous set of experiments, polyurethane catheters were impregnated with triclosan and silver carbonate, with or without salicylic acid or one of its derivatives. One set of polyurethane catheter segments were therefor dipped in a treatment solution prepared by mixing 20% v/v reagent alcohol/10% v/v ammonia (containing triclosan and silver carbonate) and 70% v/v THF (containing 93A and 60D polyurethanes), having final concentrations of 6% w/v triclosan, 0.4% w/v silver carbonate, 3% w/v 93A polyurethane and 1% w/v 60D polyurethane. Three other sets

Agents in Treatment Solution	Zones of Inhibition (mm) against *P. aeruginosa*	
	LVAD DriveLine	Polyurethane Catheters
0.5% Salicylc Acid	-	0
0.5% Acetylsalicylic Acid	-	0
0.5% Paraaminosalicylic Acid	-	0

18.0 EXAMPLE: ANTI-MICROBIAL EFFICACY OF COMBINATIONS OF SILVER SALTS AND CHLORINATED PHENOLIC COMPOUNDS

Silver compounds, in particular silver salts and various phenolic compounds were combined to study prolonged anti-microbial efficacy of the various compositions. Catheter segments for study were prepared by treating a polyurethane catheter segment in a solution of 3% 93A polyurethane and 1% 60D polyurethane, having final concentrations of agents set forth in Table 20. Then segments were placed on petri dishes seeded with *Pseudomonas aeruginosa*. Table 3 illustrates the zones of inhibition of *Pseudomonas aeruginosa* over a three day period of Ag_2CO_3 and Ag_2CO_3 in combination with three phenolic compositions, (1) parachlorometaxylenol (PCMX), (2) o-phenyl phenol and (3) p-tertiary amyl phenol, and compared their respective efficacy to triclosan and Ag_2CO_3. As shown in Table 20 it appears that a synergistic effect occurs when chlorinated phenols are combined with silver salt exhibiting prolonged anti-microbial activity.

material on a trypticase soy agar plate seeded with 0.3 ml of 10^8 cfu/ml bacterial culture and incubating at 37°C for 24 hours.. In addition, the amount of triclosan present per centimeter of catheter was determined spectrophotometrically. The results are shown in Table 21.

TABLE 21

Compounds in Treatment Solution	µg TC/cm	Zones of Inhibition (mm) vs. S. epidermidis	vs. P. aeruginosa
6% TC + 0.4% Ag_2CO_3 + 3% 93A PU + 1% 60D PU	425	11	6.5
6% TC + 0.4% Ag_2CO_3 + 3% 60D PU + 2% PVP	397	18	10

In other experiments, the effect of PVP incorporated into a hydrophobic article, *i.e.*, Dacron material for LVAD drive lines, was determined. In particular, pieces of Dacron were uniformly spread with one of the two following treatment solutions:

(iii) a treatment solution prepared by mixing 10% v/v reagent alcohol (containing triclosan, chlorhexidine diacetate (CHA), chlorhexidine free base (CHX) and silver sulfadiazine) with 90% v/v THF (containing 93A and 60D polyurethanes), having final concentrations of 0.2% w/v triclosan, 0.3% w/v chlorhexidine diacetate, 0.2% w/v chlorhexidine free base, 0.2% w/v silver sulfadiazine, 4% w/v 93A polyurethane, and 1% w/v 60D polyurethane, or

(iv) a treatment solution prepared by mixing 10% v/v reagent alcohol (containing triclosan, chlorhexidine diacetate (CHA), chlorhexidine free base (CHX) and silver sulfadiazine) with 90% v/v THF (containing 93A and 60D polyurethanes and PVP and polyvinylchloride ("PVC")), having final concentrations of 0.2% w/v triclosan, 0.3% w/v chlorhexidine diacetate, 0.2% w/v chlorhexidine free base, 0.2% w/v silver sulfadiazine, 4% w/v 93A polyurethane, 1% w/v 60D polyurethane, 2% w/v PVP and 4% w/v PVC.

CLAIMS

1. An anti-infective medical article prepared by exposing a polymer-containing medical article, for an effective period of time, to a treatment solution comprising between about 0.3 and 1.5 percent of a silver salt and between about 0.1 and 20 percent triclosan, where the treatment solution and the medical article do not contain chlorhexidine or a chlorhexidine salt.

2. The anti-infective medical article of claim 1, where the treatment solution further comprises an organic acid at a concentration of between about 0.1 and 5 percent.

3. The anti-infective medical article of claim 2, where the organic acid is citric acid.

4. The anti-infective medical article of claim 1, where the treatment solution further comprises an anti-inflammatory agent, at a concentration of between about 1 and 5 percent.

5. The anti-infective medical article of claim 4, where the anti-inflammatory agent is salicylic acid or a derivative thereof.

6. The anti-infective medical article of claim 1, where the treatment solution further comprises an additional antimicrobial agent.

7. The anti-infective medical article of claim 6, where the additional antimicrobial agent is selected from the group consisting of gramicidin, polymixin, norfloxacin, sulfamylon, polyhexamethylene biguanide, alexidine, benzalkonium chloride and rifampicin.

16. The method of claim 11, where the treatment solution further comprises an additional antimicrobial agent.

17. The method of claim 14, where the additional antimicrobial agent is selected from the group consisting of gramiciain, polymixin, norfloxacin, sulfamylon, polyhexamethylene biguanide, alexidine, benzalkonium chloride and rifampicin.

18. The method of claim 11, where the treatment solution further comprises between about 1 and 5 percent of one or more hydrophilic or hydrophobic polymer.

19. The method of claim 11, where the polymer-containing medical article is a polytetrafluoroethylene patch.

20. An anti-infective medical article prepared by exposing a polymer-containing medical article, for an effective period of time, to a treatment solution comprising between about 0.3 and 1.5 percent of a silver compound and between about 0.1 and 20 percent of a chlorinated phenol, where the chlorinated phenol is not triclosan.

21. The anti-infective medical article of claim 20, where the chlorinated phenol is parachlorometaxylenol.

22. An anti-infective medical article prepared by exposing a polymer-containing medical article, for an effective period of time, to a treatment solution comprising between about 0.1 and 5 percent of a metal compound, between about 0.1 and 20 percent triclosan, and between about 0.5 and 10 percent of a hydrogel.

23. The anti-infective medical article of claim 22, where the metal compound is a silver compound.

32. A method of preparing an anti-infective medical article comprising exposing a polymer-containing medical article, for an effective period of time, to a treatment solution comprising between about 0.1 and 5 percent of a metal compound, between about 0.1 and 20 percent triclosan, and between about 0.5 and 10 percent of a hydrogel.

33. The method of claim 32, where the metal compound is a silver compound.

34. The method of claim 32, where the hydrogel comprises polyvinylpyrrolidone.

35. A method of preparing an anti-infective medical article comprising exposing a polymer-containing medical article, for an effective period of time, to a treatment solution comprising between about 0.1 and 5 percent of a silver compound, between about 0.1 and 20 percent of triclosan, and between about 1 and 5 percent of an anti-inflammatory agent.

36. The method of claim 35, where the anti-inflammatory agent is salicylic acid or a derivative thereof.

37. The method of claim 35, where the treatment solution further comprises an additional antimicrobial agent.

38. The method of claim 34, where the additional antimicrobial agent is selected from the group consisting of chlorhexidine, a chlorhexidine salt, gramicidin, polymixin, norfloxacin, sulfamylon, polyhexamethylene biguanide, alexidine, benzalkonium chloride and rifampicin.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L29/16 A61L27/54 A61L31/16 A61L17/00 A61L15/44
A61L2/18 //A61L101:02,A61L101:32,A61L101:34,A61L101:42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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